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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,971	10/04/2001	Muthiah Manoharan	ISIS-4789	3195
32650	7590	09/14/2006	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			OWENS JR, HOWARD V	
			ART UNIT	PAPER NUMBER
			1623	
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Serial No. : 09/970,971  
Applicant : Manoharan et al.  
Filing Date : October 4, 2001  
Date Mailed : September 13, 2006

## ACKNOWLEDGEMENT OF REQUEST

### *Notice of Allowance/Allowability Mailed*

The request for a corrected notice of allowance/allowability, dated June 24, 2005, has been received by the U.S. Patent and Trademark Office. A corrected notice of allowance/allowability will not be mailed, but the Office has verified the following information, and made any necessary corrections to Office computer data:

- The allowed claims are 1-13, 18 and 21-32

A. Marty Willis  
For the Office of Patent Publication



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The request for a copy of the initialed PTO 1449, dated June 24, 2005, has been received by the U.S. Patent and Trademark Office.

- Requested copy attached

A handwritten signature in cursive script that reads "A. Marty Willis".

A. Marty Willis  
For the Office of Patent Publication



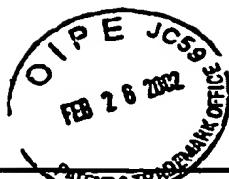
Sheet 1 of 21

<b>Form PTO-1449 Modified</b>		<b>Docket No.</b> ISIS-4789	<b>Serial No.</b> 09/970,971
<b>List of Patent and Publications Cited by Applicant (Use several sheets if necessary)</b>  <b>U.S. Department of Commerce Patent and Trademark Office</b>		<b>Applicant</b> Manoharan et al.	
		<b>Filing Date</b> October 4, 2001	<b>Group</b> Not yet assigned
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
OK	AA	Abe, A. et al., "Conformational Energies and the Random-Coil Dimensions and Dipole Moments of Polyoxides $\text{CH}_3\text{O}[(\text{CH}_2)_y\text{O}]_x\text{CH}_3$ ," <i>J. Am. Chem. Soc.</i> , 1976, 6468-6476	
	AB	Albert, P.R. et al., "Antisense knockouts: molecular scalpels for the dissection of signal transduction", <i>Trends Pharmacol. Sci.</i> , 1994, 15, 250-254	
	AC	Altmann, K. et al., "Second Generation Antisense Oligonucleotides-Inhibition of Pkc-1 And c-RAF Kinase Expression by Chimeric Oligonucleotides Incorporating 6-Substituted Carbocyclic Nucleosides and 2'-O-Ethylene Glycol Substituted Ribonucleosides," <i>Nucleosides &amp; Nucleotides</i> , 1997, 16(7-9), 917-926	
	AD	Altmann, K. et al., "Second-Generation Antisense Oligonucleotides: Structure-Activity Relationships and the Design of Improved Signal-Transduction Inhibitors", <i>Biochem. Soc. Trans.</i> , 1996, 24, 630-637	
	AE	Altmann, K. et al., "Second Generation of Antisense Oligonucleotides: From Nuclease Resistance to Biological Efficacy in Animals," <i>Chimia</i> , 1996, 50, 168-176	
	AF	Baker, B.F. et al., "2'-O-(2-Methoxy)ethyl-modified Anti-intercellular Adhesion Molecule 1 (ICAM-1) Oligonucleotides Selectively Increase the ICAM-1 Translation Initiation Complex in Human Umbilical Vein Endothelial Cells", <i>J. Biol. Chem.</i> , 1997, 272, 11994-12000	
	AG	Beal, P. A. et al., "Second Structural Motif for Recognition of DNA by Oligonucleotide-Directed Triple-Helix Formation," <i>Science</i> , 1991, 251, 1360-1363	
	AH	Beaucage, S.L. et al., "Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach", <i>Tetrahedron</i> , 1992, 48, 2223-2311	
	AI	Berger et al., "Crystal structures of B-DNA with incorporated 2'-deoxy-2'-fluoro-arabino-furanosyl thymine: implications of conformational preorganization for duplex stability," <i>Nucl. Acids Res.</i> , 1998, 26(10), 2473-2480	
OK	AJ	Berkow et al. (eds.), <i>The Merck Manual of Diagnosis and Therapy</i> , 15th Edition, Rahway, N.J., 1987, 2263-2277	
<b>EXAMINER</b> G. Karim		<b>DATE CONSIDERED</b> 5/10/06	



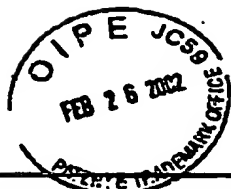
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
<b>GLC</b>	<b>AK</b>	Berkow et al. (eds.), <i>The Merck Manual of Diagnosis and Therapy</i> , 15th Edition, Rahway, N.J., 1987, 2283-2287	
	<b>AL</b>	Berkow et al. (eds.), <i>The Merck Manual of Diagnosis and Therapy</i> , 15th Edition, Rahway, N.J., 1987, 2286-2293	
	<b>AM</b>	Berkow et al. (eds.), <i>The Merck Manual of Diagnosis and Therapy</i> , 15th Edition, Rahway, NJ, 1987, 2301-2310	
	<b>AN</b>	Bernhard, E.J. et al., "Direct Evidence Linking Expression of Matrix Metalloproteinase 9 (92-kDa gelatinase/collagenase) to the metastatic phenotype in transformed rat embryo cells," <i>Proc. Natl. Acad. Sci. USA</i> , 1994, 91, 4293-4297	
	<b>AO</b>	Birkedal-Hansen, H. et al., "Proteolytic Remodeling of Extracellular Matrix," <i>Curr. Op. Cell Biol.</i> , 1995, 7, 728-735	
	<b>AP</b>	Bock, L. C. et al., "Selection of Single-Stranded DNA Molecules that Bind and Inhibit Human Thrombin," <i>Nature</i> , 1992, 355, 564-566	
	<b>AQ</b>	Böggemeyer, E. et al., "Borrelia Burgdorferi Upregulates the Adhesion Molecules E-selectin, P-selectin, ICAM-1 and VCAM-1 on Mouse Endothelioma Cells in vitro," <i>Cell Adhes. Commun.</i> , 1994, 2, 145-157	
	<b>AR</b>	Conte, M. R. "Confirmational Properties and Thermodynamics of the RNA Duplex r(CGCAAUUUGCG)2: Comparison with the DNA Analogue d(CGCAAATTTGCG)2," <i>Nucl. Acids Res.</i> , 1997, 25(13), 2627-2634	
	<b>AS</b>	Cornell, W. D. et al., "A Second Generation Force Field for the Simulation of Proteins, Nucleic Acids, and Organic Molecules," <i>J. Am. Chem. Soc.</i> , 1995, 117, 5179-5197	
<b>GLC</b>	<b>AT</b>	Cory, A.H. et al., "2'-Deoxy-2'-Methylene Derivatives of Adenosine, Guanosine, Tubercidin, Cytidine and Uridine as Inhibitors of L1210 Cell Growth in Culture," <i>Biochem. Pharmacol.</i> , 1994, 47(2), 365-371	
<b>EXAMINER</b> <i>G. Kozin</i>		<b>DATE CONSIDERED</b> 5/10/06	

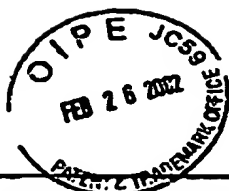


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Elc	AU	Cowser, L. M. et al., "In vitro and In Vivo Activity of Antisense Inhibitors of ras: Potential for Clinical Development," <i>Anti-Cancer Drug Design</i> , 1997, 12, 359-371	
	AV	Crooke, S.T. et al., "Pharmacokinetic Properties of Several Novel Oligonucleotide Analogs in mice", <i>J. Pharmacol. Exp. Therapeutics</i> , 1996, 277, 923-937	
	AW	Crooke, S.T. et al., "Kinetic characteristics of <i>Escherichia coli</i> RNase H1: cleavage of various antisense oligonucleotide-RNA duplexes", <i>Biochem. J.</i> , 1995, 312, 599-608	
	AX	Crooke, S. T. , "Progress in Antisense Therapeutics," <i>Medicinal Research Reviews</i> , 1996, 16(4), 319-344	
	AY	Damha, M.J. et al., "An improved procedure for derivatization of controlled-pore glass beads for solid-phase oligonucleotide synthesis", <i>Nucl. Acids Res.</i> , 1990, 18, 3813-3821	
	AZ	Damha et al., "Hybrids of RNA and Arabinonucleic Acids (ANA and 2'-ANA) Are Substrates of Ribonuclease H," <i>J. Am. Chem. Soc.</i> , 1998, 120, 12976-12977	
	BA	De Mesmaeker, A. et al., "Antisense Oligonucleotides", <i>Acc. Chem. Res.</i> , 1995, 28, 366-374	
	BB	Dean, N.M. et al., "Inhibition of protein kinase C- $\alpha$ expression in mice after systemic administration of phosphorothioate antisense-oligodeoxynucleotides", <i>Proc. Natl. Acad. Sci.</i> , 1994, 91, 11762-11766	
	BC	DeLisser, H. M. et al., "Molecular and Functional Aspects of PECAM-1/CD31," <i>Immunol. Today</i> , 1994, 15(10), 490-494	
	BD	Dimock, S. et al., "An Efficient Multigram Synthesis of Monomers for the Preparation of Novel Oligonucleotides Containing Isosteric Non-Phosphorous Backbones," <i>Nucleosides &amp; Nucleotides</i> , 1997, 16(7-9), 1629-1632	
	BE	Downward, J. et al., "The ras Superfamily of Small GTP-binding proteins," <i>TIBS</i> , 15, 1990, 469-472	
	BF	Egli, M. et al., "RNA Hydration: A Detailed Look," <i>Biochemistry</i> , 1996, 35, 8489-8494	
GL	BG	Englisch, U. et al., "Chemically Modified Oligonucleotides as Probes and Inhibitors", <i>Angew. Chem. Int. Ed. Eng.</i> , 1991, 30, 613-629	
<b>EXAMINER</b> G. Krishnan		<b>DATE CONSIDERED</b> 5/10/00	



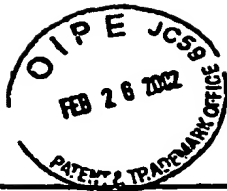
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6k	BH	Fedoroff, O. Y. et al., "Structure of a DNA: RNA Hybrid Duplex Why Rnase H Does Not Cleave Pure RNA," <i>J. Mol. Biol.</i> , 1993, 233, 509-523	
	BI	Flanagan et al., "Cellular penetration and antisense activity by a phenoxazine-substituted heptanucleotide," <i>Nat. Biotechnol.</i> , 1999, 17(1), 48-52	
	BJ	Fraser, A. et al., "Synthesis and Conformational Properties of 2'-Deoxy-2'-methylthio-pyrimidine and -purine Nucleosides: Potential Antisense Applications," <i>J. Heterocycl. Chem.</i> , 1993, 30, 1277-1287	
	BK	Freier, S.M. et al., "The ups and downs of nucleic acid duplex stability: structure-stability studies on chemically-modified DNA:RNA duplexes", <i>Nucl. Acids Res.</i> , 1997, 25, 4429-4443	
	BL	Gaffney, B.L. et al., "A New Strategy for the Protection of Deoxyguanosine During Oligonucleotide Synthesis", <i>Tetrahedron Letts.</i> , 1982, 23, 2257-2260	
	BM	Gao, Y-G. et al., "Molecular Structure of a DNA Decamer Containing an Anticancer Nucleoside Arabinosylcytosine: Conformational Perturbation by Arabinosylcytosine in B-DNA," <i>Biochem.</i> , 1991, 30(41), 9922-9931	
	BN	Gmeiner, W.H. et al., "Effect of Cytarabine on the NMR Structure of a Model Okazaki Fragment from the SV40 Genome," <i>Biochem.</i> , 1999, 38, 1166-1175	
	BO	Gonzalez, C. et al., "Structure and Dynamics of a DNA-RNA Hybrid Duplex with a Chiral Phosphorothioate Moiety: NMR and Molecular Dynamics with Conventional and Time-Averaged Restraints," <i>Biochemistry</i> , 1995, 34, 4969-4982	
	BP	Gotfredsen, C.H. et al., "Novel Oligodeoxynucleotide Analogues Containing A 2'-O-Methylarabinonucleoside," <i>Tetra. Lett.</i> , 1994, 35(37), 6941-6944	
	BQ	Gotfredsen, C.H. et al., "Synthesis and Properties of $\alpha$ - and $\beta$ -Oligodeoxynucleotides Containing $\alpha$ - and $\beta$ -1-(2-O-Methy-D-arabino-furanosyl)thymine," <i>Bioorg. Med. Chem.</i> , 1996, 4(8), 1217-1225	
6k	BR	Gotfredsen, C.H. et al., "Structure of a DNA Duplex Containing a Single 2'-O-Methyl- $\beta$ -D-araT: Combined Use of NMR, Restrained Molecular Dynamics, and Full Relaxation Matrix Refinement," <i>Bioconjugate Chem.</i> , 1996, 7, 680-688	
<b>EXAMINER</b>		DATE CONSIDERED 5/6/00	



Sheet 5 of 21

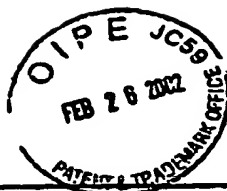
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
Glk	BS	Griffin, L. C. et al., "In Vivo Anticoagulant Properties of a Novel Nucleotide-Based Thrombin Inhibitor and Demonstration of Regional Anticoagulation in Extracorporeal Circuits," <i>Blood</i> , 1993, 81, 3271-3276	
	BT	Griffiths, C.E.M. et al., "Keratinocyte Intercellular Adhesion Molecule-1 (ICAM-1) Expression Precedes Dermal T Lymphocyte Infiltration in Allergic Contact Dermatitis ( <i>Rhus dermatitis</i> )", <i>Am. J. Pathology.</i> , 1989, 135, 1045-1053	
	BU	Gum, R. et al., "Stimulation of 92-kDa Gelatinase B Promoter Activity by ras Is Mitogen-activated Protein Kinase Kinase 1-independent and Requires Multiple Transcription Factor Binding Sites Including Closely Spaced PEA3/ets and AP-1 Sequences," <i>J. Biol. Chem.</i> , 1996, 271(18), 10672-10680	
	BV	Guzaev A. et al., "Synthesis of C-Radiolabeled Oligonucleotides with a Novel Phosphoramidite Reagent," <i>Bioorg. &amp; Med. Chem. Lett.</i> , 1998, 8, 1123-1126	
	BW	Hakugawa, J. et al., "The Inhibitory Effect of Anti-Adhesion Molecule Antibodies on Eosinophil Infiltration in Cutaneous Late Phase Response in Balb/c Mice Sensitized with Ovalbumin (OVA)," <i>J. Dermatol.</i> , 1997, 24, 73-79	
	BX	Hansske, F. et al., "2' and 3'-Ketonucleosides and their <i>Arabino</i> and <i>Xylo</i> Reduction Products", <i>Tetrahedron</i> , 1984, 40, 125-135	
	BY	Hansske et al., "Nucleic Acid Related Compounds. 43. A Convenient Procedure for the Synthesis of 2' and 3'-Ketonucleosides," <i>Tetra. Lett.</i> , 1983, 24(15), 1589-1592	
	BZ	Hegemann, L. et al., "Biochemical Pharmacology of Protein Kinase C and its Relevance for Dermatology", <i>Pharmacology of the Skin</i> , 1992, Ch. 22, CRC Press, Boca Raton, 357-368	
	CA	Himelstein, B. P. et al., "Metalloproteinases in Tumor Progression: The Contribution of MMP-9," <i>Invasion &amp; Metastasis</i> , 1994-95, 14, 246-258	
	CB	Ho, V.C. et al., "Treatment of severe lichen planus with cyclosporine", <i>J. Am. Acad. Dermatol.</i> , 1990, 22, 64-68	
Glk	CC	Horton, N. C. et al., "The Structure of an RNA/DNA Hybrid: A Substrate of the Ribonuclease Activity of HIV-1 Reverse Transcriptase," <i>J. Mol. Biol.</i> , 1996, 264, 521-533	
<b>EXAMINER</b> G. Kriz		<b>DATE CONSIDERED</b> 5/10/06	





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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
<b>Gk</b>	<b>CD</b>	Hua, J. et al., "Inhibition of Matrix Metalloproteinase 9 Expression by a Ribozyme Blocks Metastasis in a Rat Sarcoma Model System," <i>Cancer Res.</i> , 1996, 56, 5279-5284	
	<b>CE</b>	Hurtenbach, U. et al., "Prednisolone Reduces Experimental Arthritis and Inflammatory Tissue Destruction in Scid Mice Infected with <i>Borrelia Burgdorferi</i> ," <i>Int. J. Immunopharmac.</i> , 1996, 18, 281-288	
	<b>CF</b>	Iribarren, A.M. et al., "Resistance to Degradation by Nucleases of (2'S)-2'-Deoxy-2'-C-methyloligonucleotides, Novel Potential Antisense Probes," <i>Antisense Res. Dev.</i> , 1994, 4(2), 95-98	
	<b>CG</b>	Iyer, R.P. et al., "The Automated Synthesis of Sulfur-Containing Oligodeoxyribonucleotides Using 3H-1,2-Benzodithiol-3-one 1,1-Dioxide as a Sulfur-Transfer Reagent", <i>J. Org. Chem.</i> , 1990, 55, 4693-4699	
	<b>CH</b>	Jaishree, T.N. et al., "Structural Influence of RNA Incorporation in DNA: Quantitative Nuclear Magnetic Resonance Refinement of d(CG)r(CG)d(CG) and d(CG)r(C)d(TAGCG)," <i>Biochem.</i> , 1993, 32, 4903-4911	
	<b>CI</b>	Kabanov, A.V., "A new class of antivirals: antisense oligonucleotides combined with a hydrophobic substituent effectively inhibit influenza virus reproduction and synthesis of virus-specific proteins in MDCK cells", <i>FEBS Letts.</i> , 1990, 259, 327-330	
	<b>CJ</b>	Katocs, A.S. et al., "Biological Testing", <i>Remington's Pharmaceutical Sciences</i> , 18th Ed., Gennaro (ed.), Mack Publishing Co., Easton, PA, 1990, Ch. 27, 484-494	
	<b>CK</b>	Kerr, L. D. et al., "TGF-β1 Inhibition of Transin/Stromelysin Gene Expression Is Mediated Through a Fos Binding Sequence," <i>Cell</i> , 1990, 61, 267-278	
	<b>CL</b>	Kerr, L. D. et al., "Growth Factors Regulate Transin Gene Expression by c-fos-Dependent and c-fos-Independent Pathways," <i>Science</i> , 1988, 242, 1424-1427	
	<b>CM</b>	Kois, P. et al., "Synthesis and Some Properties of Modified Oligonucleotides. 2. Oligonucleotides Containing 2'-Deoxy-2'-Fluoro-β-D-Arabinofuranosyl Pyrimidine Nucleosides," <i>Nucleosides Nucleotides</i> , 1993, 12(10), 1093-1109	
<b>Gk</b>	<b>CN</b>	Kroschwitz, J.I., "Polynucleotides", <i>Concise Encyclopedia of Polymer Science and Engineering</i> , 1990, John Wiley & Sons, New York, 858-859	
<b>EXAMINER</b> <i>G. K. L.</i>		<b>DATE CONSIDERED</b> <i>5/14/06</i>	



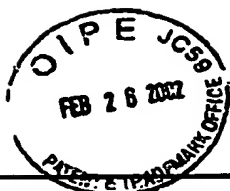
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Ck	CO	Lane, A. N. et al., "NMR Assignments and Solution Conformation of the DNA-RNA Hybrid Duplex d(GTGAACCTT)-r(AAGUUCAC)," <i>Eur. J. Biochem.</i> , 1993, 215, 297-306	
	CP	Lesnik, E.A. et al., "Oligodeoxynucleotides Containing 2'-O-Modified Adenosine" Synthesis and Effects on Stability of DNA:RNA Duplexes", <i>Biochem.</i> , 1993, 32, 7832-7838	
	CQ	Lesnik, E. A. et al., "Relative Thermodynamic Stability of DNA, RNA, and DNA: RNA Hybrid Duplexes: Relationship with Base Composition and Structure," <i>Biochemistry</i> , 1995, 34(34), 10807-10815	
	CR	Letsinger, R.L. et al., "Cholesteryl-conjugated oligonucleotides: Synthesis, properties and activity as inhibitors of replication of human immunodeficiency virus in cell culture", <i>Proc. Natl. Acad. Sci.</i> , 1989, 86, 6553-6556	
	CS	Lima et al., "Binding Affinity and Specificity of <i>Escherichia coli</i> RNase H1: Impact on the Kinetics of Catalysis of Antisense Oligonucleotide - RNA Hybrids," <i>Biochemistry</i> , 1997, 36, 390-398	
	CT	Lin et al., "A Cytosine Analogue Capable of Clamp-Like Binding to a Guanine in Helical Nucleic Acids," <i>J. Am. Chem. Soc.</i> , 1998, 120, 8531-8532	
	CU	Lisby, S. et al., "Intercellular adhesion molecule-1 (ICAM-1) expression correlated to inflammation", <i>Br. J. Dermatol.</i> , 1989, 120, 479-484	
	CV	Litwin, M. et al., "Novel Cytokine-independent Induction of Endothelial Adhesion Molecules Regulated by Platelet/Endothelial Cell Adhesion Molecule (CD31)," <i>J. Cell Biol.</i> , 1997, 139(1), 219-228	
	CW	Manoharan, M. et al., "Lipidic Nucleic Acids", <i>Tetrahedron Letts.</i> , 1995, 36, 3651-3654	
	CX	Manoharan M. et al., "Cholic Acid-Oligonucleotide Conjugates for Antisense Applications", <i>Bioorganic Med. Chem. Letts.</i> , 1994, 4, 1053-1060	
Ck	CY	Manoharan M. et al., "Oligonucleotide Conjugates: Alteration of the Pharmacokinetic Properties of Antisense Agents", <i>Nucleosides and Nucleotides</i> , 1995, 14, 969-973	
EXAMINER <b>G. Krizan</b>		DATE CONSIDERED <b>5/10/06</b>	



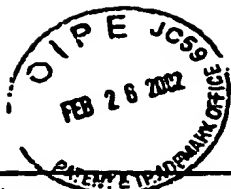
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
Gr	CZ	Manoharan, M. et al., "Chemical Modifications to Improve Uptake and Bioavailability of Antisense Oligonucleotides", <i>Annals NY Acad. Sciences</i> , 1992, 660, 306-309	
	DA	Manoharan, M. et al., "Introduction of a Lipophilic Thioether Tether in the Minor Groove of Nucleic Acids for Antisense Applications", <i>Bioorg. Med. Chem. Letts.</i> , 1993, 3, 2765-2770	
	DB	Martin, P., "Ein neuer Zugang zu 2'-O-Alkylribonucleosiden und Eigenschaften deren Oligonucleotide", <i>Helvetica Chimica Acta</i> , 1995, 78, 486-504	
	DC	Matsuda, A. et al., "Nucleosides and Nucleotides. 97. Synthesis of New Broad Spectrum Antineoplastic Nucleosides, 2'-Deoxy-2'-methylidenecytidine (DMDC) and Its Derivatives," <i>J. Med. Chem.</i> , 1991, 34, 812-819	
	DD	Miller, P.S. et al., "A New approach to chemotherapy based on molecular biology and nucleic acid chemistry: Matagen (masking tape for gene expression)", <i>Anti-Cancer Drug Des.</i> , 1987, 2, 117-128	
	DE	Milligan, J. F. et al., "Current Concepts in Antisense Drug Design," <i>J. Med. Chem.</i> , 1993, 36(14), 1923-1937	
	DF	Mishra, R.K. et al., "Improved leishmanicidal effect of phosphorothioate antisense oligonucleotides by LDL-mediated delivery", <i>Biochim. et Biophysica</i> , 1995, 1264, 229-237	
	DG	Monia, B.P. et al., "Sequence-specific Antitumor Activity of a Phosphorothioate Oligodeoxyribonucleotide Targeted to Human C-raf Kinase Supports an Antisense Mechanism of Action In Vivo," <i>Proc. Natl. Acad. Sci. USA</i> , 1996, 93, 15481-15483	
	DH	Newman, P. J. et al., "Perspective Series: Cell Adhesion in Vascular Biology," <i>Biology PECAM-1, J. Clin. Invest.</i> , 1997, 99(1), 3-7	
Gr	DI	Nies, A.S. et al., "Principles of Therapeutics", <i>Goodman &amp; Gilman's The Pharmacological Basis of Therapeutics</i> , 9th Ed., Hardman et al. (eds.), McGraw-Hill, New York, NY, 1996, Ch. 3, 43-62	
<b>EXAMINER</b> G. Karis		<b>DATE CONSIDERED</b> 5/10/06	



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<b>Form PTO-1449 Modified</b>		<b>Docket No.</b> ISIS-4789	<b>Serial No.</b> 09/970,971
<b>List of Patent and Publications Cited by Applicant (Use several sheets if necessary)</b>  <b>U.S. Department of Commerce Patent and Trademark Office</b>		<b>Applicant</b> Manoharan et al.	
		<b>Filing Date</b> October 4, 2001	<b>Group</b> Not yet assigned
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
OK	DJ	Oberhauser, B. et al., "Effective incorporation of 2'-O-methyl-oligonucleotides into liposomes and enhanced cell association through modification with thiocholesterol", <i>Nucl. Acids Res.</i> , 1992, 20, 533-538	
	DK	Obika et al., "Preparation and Properties of 2',5'-Linked Oligonucleotide Analogues Containing 3'-O, 4'-C-Methyleneribonucleosides," <i>Bioorg. Med. Chem. Lett.</i> , 1999, 9, 515-518	
	DL	Pon, R.T., "Solid Phase Supports for Oligonucleotide Synthesis", <i>Methods in Molecular Biology, Vol. 20, Protocols for Oligonucleotides and Analogs</i> , Agrawal, S. (ed.), Humana Press, Totowa, NJ, 1993, Chapter 19, 465-496	
	DM	Regezi, J. A. et al., "Vascular Adhesion Molecules in Oral Lichen Planus," <i>Oral Surg. Oral Med. Oral Pathol.</i> , 1996, 81, 682-690	
	DN	Resmini, M. et al., "Synthesis of an Arabinonucleic Acid (tANA)," <i>Bioorg. Med. Chem. Lett.</i> , 1994, 4(16), 1909-1912	
	DO	Resmini, M. et al., "38. Nucleosides: Part LV: Efficient Synthesis of Arabinoguanosine Building Blocks," <i>Helv. Chim. Acta</i> , 1994, 77, 429-434	
	DP	Resmini et al., "9. Nucleotides: Part XXXIX: Synthesis of Arabinonucleoside Phosphoramidite Building Blocks," <i>Helv. Chim. Acta</i> , 1993, 76, 158-167	
	DQ	Roberts, D. D. et al., "Neighboring Methoxy Group Effect in Solvolysis Reactions of Cyclopentyl and Cyclohexyl p-Toluenesulfonates," <i>J. Org. Chem.</i> , 1997, 62, 1857-1859	
	DR	Roberts, D. D. et al., "Neighboring-Group Study in Solvolyses of Cyclopentyl and Cyclohexyl Tosylates," <i>Cyclopentyl and Cyclohexyl Tosylates</i> , 1969, 34(8), 2415-2417	
	DS	Robins, M.J. et al., "Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2'-Deoxynucleosides", <i>J. Am. Chem. Soc.</i> , 1983, 105, 4059-4065	
OK	DT	Rosenthal et al., "Nucleosides of Branched-Chain Nitromethyl, Cyanomethyl, and Aminomethyl Sugars," <i>Tetra. Lett.</i> , 1970, 48, 4233-4235	
<b>EXAMINER</b> G. Krishnan		<b>DATE CONSIDERED</b> 5/10/06	

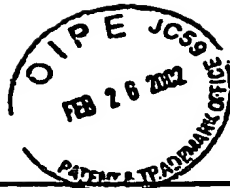


<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		Docket No. <b>ISIS-4789</b>	Serial No. <b>09/970,971</b>
		Applicant <b>Manoharan et al.</b>	
		Filing Date <b>October 4, 2001</b>	Group <b>Not yet assigned</b>
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
GC	DU	Ruoslahti, E., "How Cancer Spreads," <i>Sci. Am.</i> , 1996, 72-77	
	DV	Saison-Behmoaras, T. et al., "Short modified antisense oligonucleotides directed against Ha-ras point mutation induce selective cleavage of the mRNA and inhibit T24 cells proliferation", <i>EMBO J.</i> , 1991, 10, 1111-1118	
	DW	Sanghvi, Y.S. et al., "Concept, Discovery and Development of MMI Linkage: Story of a Novel Linkage for Antisense Constructs," <i>Nucleosides &amp; Nucleotides</i> , 1997, 16(7-9), 907-916	
	DX	Schmit, C. et al., "The Effects of 2'- and 3'-Alkyl Substituents on Oligonucleotide Hybridization and Stability," <i>Bioorg. Med. Chem. Lett.</i> , 1994, 4(16), 1969-1974	
	DY	Schweitzer, B.I. et al., "Solution Structure of a DNA Dodecamere Containing the Anti-Neoplastic Agent Arabinosylcytosine: Combined Use of NMR, Restrained Molecular Dynamics, and Full Relaxation Matrix Refinement," <i>Biochem.</i> , 1994, 33(38), 11460-11475	
	DZ	Searle, M. S. et al., "On the Stability of Nucleic Acid Structures in Solution: Enthalpy-Entropy Compensations, Internal Rotations and Reversibility," <i>Nucl. Acids Res.</i> , 1993, 21(9), 2051-2056	
	EA	Seela, F. et al., "Palindromic Octa-and Dodecanucleotides Containing 2'-Deoxytubercidin: Synthesis, Hairpin Formation, and Recognition by the Endodeoxyribonuclease <i>EcoRI</i> ", <i>Biochemistry</i> , 1987, 26, 2232-2238	
	EB	Shea, R.G. et al., "Synthesis, hybridization properties and antiviral activity of lipid-oligodeoxynucleotide conjugates", <i>Nucl. Acids Res.</i> , 1990, 18, 3777-3783	
	EC	Shiohara et al., "Fixed drug Eruption: Expression of Epidermal Keratinocyte Intercellular Adhesion Molecule-1 (ICAM-1)", <i>Arch. Dermatol.</i> , 1989, 125, 1371-1376	
	ED	Stein, C.A. et al., "Oligodeoxynucleotides as Inhibitors of Gene Expression: A Review", <i>Cancer Res.</i> , 1988, 48, 2659-2668	
GC	EE	Stetler-Stevenson, W.G. et al., "Tumor Cell Interactions with the Extracellular Matrix During Invasion and Metastasis," <i>Annu. Rev. Cell Biol.</i> , Palade, G.E. et al. (eds.), 1993, 9, 541-573	
EXAMINER		G. Krishnan	DATE CONSIDERED 5/10/06



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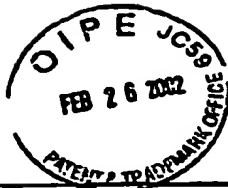
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
6X	EF	Svinarchuk, F.P. et al., "Inhibition of HIV proliferation in MT-4 cells by antisense oligonucleotide conjugated to lipophilic groups", <i>Biochimie</i> , 1993, 79, 49-54	
	EG	Swayze, E. E. et al., "The Synthesis of N,N'-O-Trisubstituted Hydroxylamines via a Mild Reductive Alkylation Procedure: An Improved Synthesis of the MMI Backbone," <i>Synlett</i> , 1997, 859-861	
	EH	Swayze, E. E. et al., "The Synthesis of the Sixteen Possible 2'-O-Methyl MMI Dimer Phosphoramidites: Building Blocks for the Synthesis of Novel Antisense Oligonucleotides," <i>Nucleosides &amp; Nucleotides</i> , 1997, 16(7-9), 971-972	
	EI	U.S. Congress, Office of Technology Assessment, "The State-of-the-art in Genetic Screening", <i>Genetic Monitoring and Screening in the Workplace</i> , OTA-BA-455, U.S. Government Printing Office, Washington, D.C., 1990, Ch. 5, 75-99	
	EJ	Uhlmann, E. et al., "Antisense Oligonucleotides: A New Therapeutic Principle", <i>Chem. Reviews</i> , 1990, 90, 543-584	
	EK	Wagner, D. et al., "Preparation and Synthesis Utility of Some Organotin Derivatives of Nucleosides", <i>J. Org. Chem.</i> , 1974, 39, 24-30	
	EL	Wagner, R. W. et al., "Antisense Gene Inhibition by Oligonucleotides Containing C-5 Propyne Pyrimidines," <i>Science</i> , 1993, 260, 1510-1513	
	EM	Wahlestedt, C. et al., "Modulation of Anxiety and Neuropeptide Y-Y1 Receptors by Antisense Oligodeoxynucleotides", <i>Science</i> , 1993, 259, 528-531	
	EN	Wahlestedt, C. et al., "Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions", <i>Nature</i> , 1993, 363, 260-263	
6K	EO	Wilds, C.J. et al., "Duplex Recognition by Oligonucleotides Containing 2'-Deoxy-2'-fluoro-D-arabinose and 2'-Deoxy-2'-fluoro-D-ribose. Intermolecular 2'-OH-Phosphate Contacts versus Sugar Puckering in the Stabilization of Triple-Helical Complexes," <i>Bioconjugate Chem.</i> , 1999, 10, 299-305	
<b>EXAMINER</b> G. K. [Signature]		<b>DATE CONSIDERED</b> 5/10/06	



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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
Gl	EP	Wolfe, S., "The Gauche Effect. Some Stereochemical Consequences of Adjacent Electron Pairs and Polar Bonds," <i>Accounts of Chemical Research</i> , 1972, 5, 102-110	
	EQ	Young, S. L. et al., "Triple Helix Formation Inhibits Transcription Elongation In Vitro," <i>Proc. Natl. Acad. Sci. USA</i> , 1991, 88, 10023-10026	
	ER	Zhang, H. et al., "Conformational Perturbation of the Anticancer Nucleoside Arabinosylcytosine on Z-DNA: Molecular Structure of (araC-dG) <sub>3</sub> at 1.3 Å Resolution," <i>Biopolymers</i> , 1992, 32, 1559-1569	
*	ES	Ausubel, F.M. et al., in <i>Current Protocols in Molecular Biology</i> , John Wiley, New York, 1989	
*	ET	Cohen in <i>Oligonucleotides: Antisense Inhibitors of Gene Expression</i> , CRC Press, Inc., Boca Raton, FL, 1989	
*	EU	Sambrook, J. et al., <i>Molecular Cloning: A Laboratory Manual</i> , Cold Spring Harbor Laboratory Press, 1989	
* Gl	EV	Sanger et al., <i>Principles of Nucleic Acid Structure</i> , Springer-Verlag, New York, NY, 1984	
<b>EXAMINER</b> G. Kristian		<b>DATE CONSIDERED</b> 5/10/06	

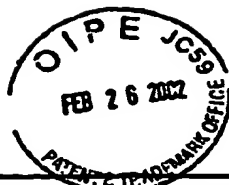
\*A copy of this reference will not be forwarded to the U.S. Patent and Trademark Office since it is believed to be too voluminous and easily obtainable by the Examiner.



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		Applicant <b>Manoharan et al.</b>	
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
<b>GL</b>	<b>EW</b>	Arnott et al., "Optimised Parameters for A-DNA and B-DNA" <i>Biochemical and Biophysical Research Communication</i> , <i>Biochem. Biophys. Res. Commun.</i> , 1970, 47, 1504-1510	
	<b>EX</b>	Beaucage, S. et al., "Deoxynucleoside Phosphoramidites - A New Class of Key Intermediates for Deoxypolynucleotide Synthesis", <i>Tetra. Lett.</i> , 1981, 22, 1859-1862	
	<b>EY</b>	Butke, G. et al., "Facile Synthesis of 2'-Amino-2'-Deoxynucleoside from the Corresponding Arabino Derivative," <i>Nucleic Acid Chemistry</i> , Townsend, L.B. et al., eds., 1986, John Wiley & Sons, New York, 149-152	
	<b>EZ</b>	Calvo-Mateo, A. et al., "3'-C-Cyano-3'-Deoxythymidine," <i>Tetra. Letts.</i> , 1988, 23, 941-944	
	<b>FA</b>	Chen, Q. Y. et al., "Studies on Fluoroalkylation and Fluoroalkoxylation. Part 33. Direct Trifluoromethylation of Aryl Halides with Fluorosulphonyldifluoromethyl Iodide in the Presence of Copper: an Electron Transfer Induced Process," <i>J. Chem. Soc. Perkin Trans. I</i> , 1989, 2385-2387	
	<b>FB</b>	Chladek, S. et al., "Facile Synthesis of 2'-Amino-2'-Deoxyadenosine", <i>J. Carbo., Nucleosides &amp; Nucleotides</i> , 1980, 7, 63-75	
	<b>FC</b>	Codington, J. F. et al., "Nucleosides. XVIII. Synthesis of 2'-Fluorothymidine, 2'-Fluorodeoxyuridine, and Other 2'-Halogeno-2'-Deoxy Nucleosides," <i>J. Org. Chem.</i> , 1964, 29, 558-564	
	<b>FD</b>	Damha, M. J. et al., "Solution and solid phase chemical synthesis of arabinonucleotides," <i>Can. J. Chem.</i> , 1989, 67, 831-839	
	<b>FE</b>	Divakar et al., "Reaction Between 2,2'-Anhydro-1- $\beta$ -D-arabinofuranosyluracil and Thiolate Ions", <i>J. Chem. Soc. Perkins Trans. I</i> , 1982, 1625-1628	
	<b>FF</b>	Divakar et al., "Approaches to the Synthesis of 2'-Thio Analogues of Pyrimidine Ribosides", <i>J. Chem. Soc. Perkins Trans. I</i> , 1990, 969-974	
<b>GL</b>	<b>FG</b>	Freskos, J.N., "Synthesis of 2'Deoxypyrimidine Nucleosides Via Copper (I) Iodide Catalysis", <i>Nucleosides &amp; Nucleotides</i> , 1989, 8, 1075-1076.	
<b>EXAMINER</b> <i>G. Krishnan</i>		<b>DATE CONSIDERED</b> <i>5/10/06</i>	



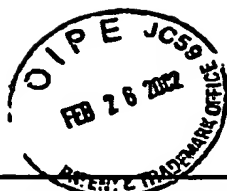


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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	<b>FH</b>	Gait, M.J. et al., <i>Oligonucleotide Synthesis A Practical Approach</i> , IRL Press, Washington, DC, 1984, Table of Contents only	
Gl	<b>FI</b>	Guschlbauer, W. et al., "Nucleoside conformation is Determined by the Electronegativity of the Sugar Substituent", <i>Nucl. Acis Res.</i> , 1980, 8, 1421	
	<b>FJ</b>	Hansske, F. et al., "2' and 3'-Ketonucleosides and their <i>Arabino</i> and <i>Xylo</i> Reduction Products," <i>Tetrahedron</i> , 1984, 40, 125-135	
	<b>FK</b>	Hertel, L.W. et al., "Synthesis of 2-Deoxy-2,2-difluoro-D-ribose and 2-Deoxy-2,2-difluoro-D-ribofuranosyl Nucleosides", <i>J. Org. Chem.</i> , 1988, 53, 2406-2409	
	<b>FL</b>	Hobbs, J. et al., "Polynucleotides Containing 2'-Chloro-2'-Deoxyribose", <i>Biochem.</i> , 1972, 11, 4336	
	<b>FM</b>	Ikehara, M., "Purine 8-Cyclonucleosides", <i>Accounts Chem. Res.</i> , 1969, 2, 47-53	
	<b>FN</b>	Ikehara et al., "Purine Cyclonucleosides-26 A Versatile Method for the Synthesis of Purine O-Cyclo-Nucleosides. The First Synthesis of 8,2'-Anhydro-8-Oxy 9-β-D-Arabinofuranosylguanine", <i>Tetrahedron</i> , 1975, 31, 1369-1372	
	<b>FO</b>	Ikehara et al., "Polynucleotides. L. synthesis and properties of poly (2'chloro-2'-deoxyadenylic acid) and poly (2'-bromo-2'-deoxyadenylic acid)", <i>Nucl. Acids Res.</i> , 1977, 4, 4249-4260	
	<b>FP</b>	Ikehara et al., "Studies of Nucleosides and Nucleotides-LXXXII. <sup>1)</sup> cyclonucleosides. (39). <sup>2)</sup> synthesis and properties of 2'halogen-2'-deoxyadenosines", <i>Chem. Pharm. Bull.</i> , 1978, 26, 2449-2453	
	<b>FQ</b>	Ikehara, M. et al., "Studies of Nucleosides and Nucleotides-LXXXIV <sup>1)</sup> ", <i>Tetrahedron</i> , 1978, 34, 1133-1138	
	<b>FR</b>	Ikehara et al., "Polynucleotides. LII. synthesis and properties of poly (2'-deox-2'-fluoroadenylic acid)", <i>Nucl. Acids Res.</i> , 1978, 5, 1877-1887	
Gl	<b>FS</b>	Hobbs, J., et al., "Polynucleotides containing 2'-Amino-2'-deoxyribose and 2'-Azido-2'-deoxyribose," <i>Biochemistry</i> , 1973, 12(25), 5138-5145	
<b>EXAMINER</b> G. Krishnan		<b>DATE CONSIDERED</b> 5/10/06	

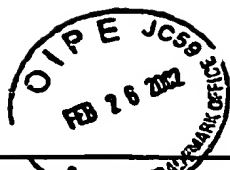


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		Filing Date <b>October 4, 2001</b>	Group <b>Not yet assigned</b>
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
<b>BK</b>	<b>FT</b>	Ikehara et al., "Polynucleotides. LVI. Synthesis and Properties of Poly(2'-deoxy-2'-fluorinosinic Acid", <i>Nucl. Acids Res.</i> , 1978, 5, 3315-3324	
	<b>FU</b>	Ikehara et al., "Studies on Nucleosides and Nucleotides. LXXXIX. Purine Cyclonucleosides. (43) Synthesis and Properties of 2'-Halogeno-2'-deoxyguanosines", <i>Chem. Pharm. Bull.</i> , 1981, 29(11), 3281-3285	
	<b>FV</b>	Hobbs, J., et al., "Poly 2'-Deoxy-2'Aminouridylic acid," <i>Biochemical and Biophysical Communications</i> , 1972, 46(4), 1509-1515	
	<b>FW</b>	Imazawa et al., "Nucleosides and Nucleotides, XII. Synthesis and Properties of 2'-Deoxy-2'-mercaptouridine and its Derivatives", <i>Chem. Pharm. Bull.</i> , 1975, 23, 604-610	
	<b>FX</b>	Inoue, H. et al., "Synthesis and hybridization studies on two complementary nona(2'-O-methyl) ribonucleotides", <i>Nucl. Acids Res.</i> , 1987, 15, 6131-6148	
	<b>FY</b>	Iyer, R. P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizing Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates," <i>J. Am. Chem. Soc.</i> , 1990, 112, 1253-1254	
	<b>FZ</b>	Jarvi, E. T. et al., "Synthesis and Biological Evaluation of Dideoxynucleosides Containing a Difluoromethylene Unit," <i>Nucleosides &amp; Nucleotides</i> , 1989, 8, 1111-1114	
	<b>GA</b>	Jones, R.A., "Transient protection: Efficient one-flask synthesis of protected deoxynucleosides", <i>J. Am. Chem. Soc.</i> , 1982, 104, 1316-1319	
	<b>GB</b>	Kazimierczuk et al., "Synthesis of 2'-deoxytubercidin, 2'-deoxyadenosine, and related 2'-deoxynucleosides via novel direct stereospecific sodium salt glycosylation procedure", <i>J. Am. Chem. Soc.</i> , 1984, 106, 6379-6382	
	<b>GC</b>	Koole et al., "Synthesis of phosphate-methylated DNA fragments using 9-fluorenylmethoxycarbonyl as transient base protecting group", <i>J. Org. Chem.</i> , 1989, 54, 1657-1664	
<b>CK</b>	<b>GD</b>	Markiewicz, W. and Wiewiorowski, "Nucleic Acid Chemistry", Part 3, pp. 229-231, Townsend, L. and Tipson, eds., J. Wiley and Sons, New York, 1986	
<b>EXAMINER</b> <i>G. Kozian</i>		<b>DATE CONSIDERED</b> <i>5/10/06</i>	



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<b>Form PTO-1449 Modified</b>		<b>Docket No.</b> ISIS-4789	<b>Serial No.</b> 09/970,971
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		<b>Filing Date</b> October 4, 2001	<b>Group</b> Not yet assigned
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
GE	Markus-Sekura et al., "Comparative Inhibition of Chloramphenicol Acetyltransferase Gene Expression by Antisense Oligonucleotide Analogues Having Alkyl Phosphotriester, Methylphosphonate and Phosphorothioate Linkages", <i>Nucl. Acids Res.</i> , 1987, 15(4), 5749-5763		
GF	Miller, P.S. et al., "A New Approach to Chemotherapy Based on Molecular Biology and Nucleic Acid Chemistry: Matagen (Masking Tape for Gene Expression)", <i>Anti-Cancer Drug Design</i> , 1987, 2, 117-128		
GG	Ohtsuka, M. et al., "Recognition by Restriction Endonuclease <i>EcoRI</i> of Deoxyoctanucleotides Containing Modified Sugar Moieties", <i>Eur. J. Biochem.</i> , 1984, 139, 447-450		
GH	Parkes, K.E.B. et al., "A Short Synthesis of 3'-Cyano-3'-Deoxythymidine", <i>Tetra. Lett.</i> , 1988, 29, 2995-2996		
GI	Ragathan, R., "Modification of the 2'-Position of Purine Nucleosides: Synthesis of 2'-a-Substituted-2'-Deoxyadenosine Analogs", <i>Tetra. Lett.</i> , 1977, 15, 1291-1294		
GJ	Rao, T. S. et al., "A Novel One-step Procedure for the Conversion of Thymidine into 2,3'-Anhydrothymidine," <i>J. Chem. Soc. Chem. Commun.</i> , 1989, 997-998		
GK	Robins, M. J. et al., "Nucleic acid related compounds: 41. Restricted furanose conformations of 3',5'-O-(1,1,3,3-tetraisopropylidisiloxy-1,3-diyl) nucleosides provide a convenient evaluation of anomeric configuration," <i>Can. J. Chem.</i> , 1983, 61, 1911-1920		
GL	Ryan et al., "Synthesis of 2-Thio-D-ribose and 2'-Thioadenosine Derivatives", <i>J. Org. Chem.</i> , 1971, 36(18), 2646-2657		
GM	Shibahara et al., "Inhibition of human immunodeficiency virus (HIV-1) replication of synthetic oligo-RNA derivatives", <i>Nucl. Acids Res.</i> , 1989, 17(1), 239-252		
GN	Sproat, B.S. et al., "Highly Efficient Chemical Synthesis of 2'-O-methyloligoribonucleotides and Tetrabiotinylated Derivatives; Novel Probes that are Resistant to Degradation by RNA or DNA Specific Nucleases", <i>Nucl. Acids Res.</i> , 1989, 17, 3373-3386		
<b>EXAMINER</b> G. K. Friedman		<b>DATE CONSIDERED</b> 5/10/06	



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<b>List of Patent and Publications Cited by Applicant (Use several sheets if necessary)</b>  <b>U.S. Department of Commerce Patent and Trademark Office</b>		<b>Applicant</b> Manoharan et al.	
		<b>Filing Date</b> October 4, 2001	<b>Group</b> Not yet assigned
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
GK	GO	Sproat, B. S. et al., "New synthetic routes to protected purine 2-O-methylriboside-3'-O-phosphoramidites using a novel alkylation procedure," <i>Nucl. Acids Res.</i> , 1990, 18, 41-49	
	GP	Uesugi, S. et al., "A Linear Relationship Between Electronegativity of 2'-Substituents and Conformation of Adenine Nucleosides," <i>Tetrahedron Letts.</i> , 1979, 42, 4073-4076	
	GQ	Uesugi et al., "Improved Synthesis of 2'-Fluoro-2'-Deoxyadenosine and Synthesis and Carbon-13 NMR Spectrum of Its 3',5'-Cyclic Phosphate Derivative", <i>Nucleosides &amp; Nucleotides</i> , 1983, 2, 373-385	
	GR	Uhlmann et al., "Antisense Oligonucleotides: A New Therapeutic Principle", <i>Chem. Rev.</i> , 1990, 558	
	GS	Zon, G., "Oligonucleotide analogues as potential chemotherapeutic agents," <i>Pharmaceutical Res.</i> , 1988, 5(9), 539-547	
	GT	Cheatham, T. E. et al., "Molecular Dynamics Simulations Highlight the Structural Differences among DNA:DNA, RNA:RNA, and DNA:RNA Hybrid Duplexes," <i>J. Am. Chem. Soc.</i> , 1997, 119, 4805-4825	
	GU	Jaishree, T. N. et al., "Structural Influence of RNA Incorporation in DNA: Quantitative Nuclear Magnetic Resonance Refinement of d (CG)r(CG)d(CG) and d(CG)r(C)d(TAGCG)," <i>Biochemistry</i> , 1993, 32, 4903-4911	
GRC	GV	Nishizaki, T. et al., "Solution Structures of DNA Duplexes Containing a DNA•RNA Hybrid Region, d(GG)r(AGAU)d(GAC)•d(GTCATCTCC) and d(GGAGA)r(UGAC)•d(GTCATCTCC) <sup>1-4</sup> ," <i>Biochemistry</i> , 1996, 35, 4016-4025	
<b>EXAMINER</b> G. Krishna		<b>DATE CONSIDERED</b> 5/10/06	



<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office	Docket No. <b>ISIS-4789</b>	Serial No. <b>09/970,971</b>
	Applicant <b>Manoharan et al.</b>	
	Filing Date <b>October 4, 2001</b>	Group <b>Not yet assigned</b>

**U. S. PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Name	Class	Subclass
<i>PK</i>	GW	3,687,808	08/29/72	Merigan et al.	195	28
	GX	4,689,320	08/25/87	Kaji	514	44
	GY	4,806,463	02/21/89	Goodchild et al.	435	5
	GZ	5,004,810	04/02/91	Draper	536	27
	HA	5,166,195	11/24/92	Ecker	514	44
	HB	5,194,428	03/16/93	Agrawal et al.	514	44
	HC	5,212,295	05/18/93	Cook	536	26.7
	HD	5,242,906	09/07/93	Pagano et al.	514	44
	HE	5,248,670	09/28/93	Draper et al.	514	44
	HF	5,442,049	08/15/95	Anderson et al.	536	24.5
	HG	5,457,189	10/10/95	Crooke et al.	536	24.5
	HH	5,514,577	05/07/96	Draper et al.	435	238
	HI	5,514,788	05/07/96	Bennett et al.	536	23.1
<i>PK</i>	HJ	5,523,389	06/04/96	Ecker et al.	536	23.1

**FOREIGN PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Country	Translation YES NO	
<i>PK</i>	HK	WO 89/12060	12/14/89	PCT		
<i>PK</i>	HL	WO 94/08003	04/14/94	PCT		
<i>PK</i>	HM	WO 92/03568	03/05/92	PCT		

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				Applicant <b>Manoharan et al.</b>			
				Filing Date <b>October 4, 2001</b>		Group <b>Not yet assigned</b>	
<b>U. S. PATENT DOCUMENTS</b>							
Examiner Initial		Document No.	Date	Name	Class	Subclass	
<i>GK</i>	HN	5,580,767	12/03/96	Cowsert et al.	435	172.3	
	HO	5,582,972	12/10/96	Lima et al.	435	6	
	HP	4,381,344	04/1983	Rideout et al.	435	87	
	HQ	5,013,830	05/07/91	Ohtsuka et al.	536	27	
	HR	5,134,066	07/28/92	Rogers et al.	435	91	
	HS	5,212,295	05/18/93	Cook	536	26.7	
	HT	5,214,135	05/25/93	Srivastava et al.	536	26.7	
	HU	5,466,786	11/14/95	Buhr et al.	536	26.26	
	HV	5,658,731	08/19/97	Sproat et al.	435	6	
	HW	5,672,695	09/30/97	Eckstein et al.	536	24.5	
<i>GK</i>	HX	5,698,687	12/16/97	Eckstein et al.	536	25.3	
<b>FOREIGN PATENT DOCUMENTS</b>							
Examiner Initial		Document No.	Date	Country	Translation YES NO		
<i>GK</i>	HY	2,017,369	05/23/90	Canada	X		
<i>GK</i>	HZ	0 260 032	08/27/87	EP	X		
<i>GK</i>	IA	0 287 313	10/19/88	EP	X		
	IB	0 399 330	05/15/90	EP		X	
<i>GK</i>	IC	0 417 999	03/10/91	EP	X		
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	Filing Date <b>October 4, 2001</b>	Group <b>Not yet assigned</b>

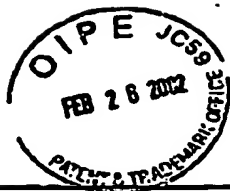
**U. S. PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Name	Class	Subclass
GK	ID	5,245,022	09/14/93	Weis et al.	536	24
	IE	5,627,053	05/06/97	Usman et al.	435	91
	IF	5,639,647	06/17/97	Usman et al.	435	199
	IG	5,817,635	10/06/98	Eckstein et al.	514	44
GK	IH	5,859,221	01/12/99	Cook et al.	536	23

**FOREIGN PATENT DOCUMENTS**

Examiner Initial		Document No.	Date	Country	Translation YES NO	
GK	II	39 15462 A1	06/09/90	Germany	considered German English Abstract	X
	IJ	41 10085 A1	10/01/92	Germany	considered German English Abstract	X
	IK	WO 90/15814	12/27/90	PCT	X	
	IL	WO 91/06556	05/16/91	PCT	X	
	IM	WO 91/15499	10/17/91	PCT	considered German English Abstract	X
	IN	WO 92/07065	04/30/92	PCT	X	
	IO	339 842	11/02/89	EP		
	IP	0 552 178 B1	01/02/97	EP		
GK	IQ	1 205 021	05/27/86	Canada		

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				Applicant Manoharan et al.			
				Filing Date October 4, 2001		Group Not yet assigned	
<b>U. S. PATENT DOCUMENTS</b>							
Examiner Initial		Document No.	Date	Name	Class	Subclass	
EC	IR	5,582,986	12/10/96	Monia et al.	435	6	
	IS	5,591,600	01/07/97	Ecker	435	69.1	
	IT	5,591,623	01/07/97	Bennett et al.	435	240.2	
	IU	5,591,720	01/07/97	Anderson et al.	514	44	
	IV	5,607,923	03/04/97	Cook et al.	514	44	
	IW	5,620,963	04/15/97	Cook et al.	514	44	
	IX	5,639,649	06/17/97	Almond et al.	435	235.1	
	IY	5,658,891	08/19/97	Draper et al.	514	44	
	IZ	5,661,134	08/26/97	Cook et al.	514	44	
	JA	5,681,747	10/28/97	Boggs et al.	435	375	
	JB	5,681,944	10/28/97	Crooke et al.	536	24.5	
	JC	5,877,309	03/02/99	McKay et al.	536	24.5	
	JD	5,985,558	11/16/99	Dean et al.	435	6	
	JE	5,955,443	09/21/99	Bennett et al.	514	44	
	JF	6,111,094	08/29/00	Bennett et al.	536	24.5	
	JG	5,334,711	08/02/94	Sproat, et al.	536	24.5	
	JH	6,300,491	10/09/01	Bennett et al.	536	24.5	
	JI	5,670,633	09/23/97	Cook et al.	536	23.1	
SK	JJ	6,307,040	10/23/01	Cook et al.	536	24.5	
EXAMINER <i>G. Karim</i>				DATE CONSIDERED <i>5/10/06</i>			